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Mifamurtide for High-Grade, Resectable, Nonmetastatic Osteosarcoma Following Surgical Resection: A Cost-Effectiveness Analysis

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ABSTRACT

Objectives: Mifamurtide is an immune macrophage stimulant that when added to standard chemotherapy has demonstrated survival benefit for newly diagnosed osteosarcoma. The objectives of this study were to investigate the cost-effectiveness of adding mifamurtide to standard three- or four-agent chemotherapy for high-grade, resectable, nonmetastatic osteosarcoma following surgical resection and the issues of obtaining robust cost-effectiveness estimates for ultra-orphan drugs, given the shortage of data. **Methods:** An economic evaluation was conducted from the perspective of the UK's National Health Service as part of the manufacturer's submission to the National Institute for Health and Care Excellence. The disease process was simplified to a transition through a series of health states, modeled by using a Markov approach. Data to inform the model were derived from patient-level data of Study INT-0133, published literature, and expert opinion. The final efficacy measure was life-years gained (LYG), and utilities were used to obtain quality-adjusted life-years (QALYs). **Results:** For a 60-year time frame and a discount rate of 3.5% for outcomes, patients receiving mifamurtide benefited from an average additional 1.57 years of life and 1.34 QALYs, compared with patients receiving chemotherapy alone, giving an incremental cost-effectiveness ratio (ICER) of £58,737 per LYG and £68,734 per QALY. Because treatment effects were both substantial in restoring health and sustained over a very long period, the National Institute for Health and Care Excellence changed its guidance to allow a discount of 1.5% for outcomes to be applied in these special circumstances. By using this discount factor, it was found that patients receiving mifamurtide had an average additional 2.58 years of life and 2.20 QALYs compared with patients receiving chemotherapy alone, resulting in an ICER of £35,765 per LYG and £41,933 per QALY. **Conclusion:** Mifamurtide's ICER is cost-effective compared with that of other orphan and ultra-orphan drugs, for which prices and corresponding cost-effectiveness estimates are high.

Keywords: cost-effectiveness analysis, discount rate, NICE appraisal, osteosarcoma, ultra-orphan.

Background

Osteosarcoma is the most common type of primary bone tumor and usually occurs during childhood and adolescence [1]. Its incidence varies with age, with an annual incidence rate of 7.3 cases per million for adolescents (aged 15–19 years) for the period 1988 to 1997 in the United Kingdom [2]. The disease has an estimated annual incidence rate of 2.6 cases per million for children (aged 0–14 years) for the period 1988 to 1999 [3]. These data on osteosarcoma indicate that approximately 73 children, adolescents, and young adults present with osteosarcoma per year in the United Kingdom, with 58 (80%) of these individuals having high-grade, nonmetastatic disease [4–6]. Osteosarcoma can be considered an "ultra-orphan" disease, a term used to describe very rare diseases, as distinct from more common orphan diseases. The National Institute for Health and Care Excellence (NICE) defines a disease as ultra-orphan if it has a UK prevalence of less than 1 in 50,000 and if there are fewer than 1,000 cases per year [7].

The management of patients with osteosarcoma is complex and aims to completely remove all clinically detectable tumors surgically and to control microscopic metastatic disease via systemic polychemotherapy [8]. The aim is to increase the survival rate and prevent recurrence of the disease. The treatment pathway is generally composed of neoadjuvant chemotherapy, followed by optimal surgery to remove the entire primary tumor and to render the patient disease free, with a subsequent course of adjuvant chemotherapy being administered to target micrometastases. Young people who undergo successful surgery for osteosarcoma are able to live full lives, and they have a quality of life similar to that of their peers although prosthetic limbs and endoprostheses will need to be replaced as they grow [9].

There are currently no standard recommended combinations of chemotherapy drugs, and the optimal treatment duration is yet to be defined [10]. There currently, however, are four chemotherapeutic agents with well-established efficacy in treating osteosarcoma: doxorubicin, cisplatin, high-dose methotrexate with leucovorin rescue, and ifosfamide. Currently, 60% to 70% of the patients having high-grade, nonmetastatic osteosarcoma achieve long-term, disease-free survival following these three- or four-agent neoadjuvant and adjuvant chemotherapy regimens

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[11,12]. Since the introduction of standard chemotherapy, no new drugs with proven efficacy have been added to the standard therapeutic armamentarium [8]. Various studies have suggested that the combination of multiagent chemotherapy with biologic-response modifiers and immune activators may achieve additional treatment benefits [10].

Mifamurtide is an immune macrophage stimulant. It has a marketing authorization for use in children, adolescents, and young adults for the treatment of high-grade, resectable, non-metastatic osteosarcoma after macroscopically complete surgical resection, and has been safely administered together with standard adjuvant chemotherapy in patients aged between 2 and 30 years.

The largest ever completed, randomized phase III trial of treatments for patients aged 30 years or younger with newly diagnosed osteosarcoma initiated in 1993 was reported by Meyers et al. [13,14]. Among the 793 patients who enrolled in the trial, 115 patients had either clinically detectable metastases or an unresectable primary tumor at study entry. Of the 678 remaining patients, 16 were considered ineligible. Among the remaining 662 patients without metastases and resectable tumors, 361 patients were male and 301 were female. The trial results have demonstrated a survival benefit when mifamurtide is added to a chemotherapy regimen, with the 6-year survival rates increasing from 71% to 75% for patients on three-agent chemotherapy and from 70% to 81% for patients on four-agent chemotherapy. For all patients, the overall 6-year survival rate when mifamurtide is added to a chemotherapy regimen increased from 70% to 78% ($P = 0.03$) [14]. The median age of patients in this trial was 13 years. The median follow-up duration for the trial, from commencement of the maintenance phase, was 7.7 years while the maximum follow-up duration was 12.25 years [14]. The clinical trial, despite its weaknesses in standards and procedures, provided a good source of data for an ultra-orphan disease, because of study sample size and long-term follow-up.

The cost-effectiveness of mifamurtide treatment in this patient group has not previously been published, although the manufacturer of mifamurtide recently made a submission to NICE that included a cost- effectiveness analysis for mifamurtide as an add-on to multiagent chemotherapy compared with multiagent chemotherapy alone [15]. The decision-analytic model and subsequent cost-effectiveness analysis presented here formed part of the manufacturer's submission to NICE.

Like other ultra-orphan diseases, data shortages, due to the limited number of clinical trials in osteosarcoma and difficulties with recruiting the number of patients needed to adequately power such a trial, mean that the level of uncertainty associated with clinical effectiveness for mifamurtide is greater than for drugs for prevalent diseases. Hence, this article lays out not only how the cost-effectiveness analysis was assessed but also what the difficulties were in trying to develop cost-effectiveness models in this disease area.

Methods

Model Structure

For the purposes of the economic analysis, the disease process was formulated as a transition through a series of health states, modeled by using a Markov approach (Fig. 1). The comparator treatment used for assessment of the decision problem was the three- or four-agent chemotherapy regimen alone, which represents the current UK treatment approach.

Patients entered the model in the disease-free state after surgical resection and remain in this state unless they have a recurrence or die. Following a recurrence, patients could move either to a postrecurrence disease-free state or to a postrecurrence disease-progression state. The first cycle in the disease-free state represented the chemotherapy maintenance phase, in which all patients received adjuvant chemotherapy with or without mifamurtide. This cycle had a length of 9 months. Thereafter, cycles had a length of 6 months. Patients moved among states during each cycle. Once patients entered the disease-progression state, the model made the assumption that they remained there until death. Patients in the disease-free health state at the end of the trial period (12.25 years) were assumed to have a mortality rate equivalent to that of the general population. The model used estimates of effectiveness, costs, and health-state values in these health states to model progression of disease and cost-effectiveness over time. Costs and outcomes were discounted at 3.5% per annum, in line with NICE guidance [16].

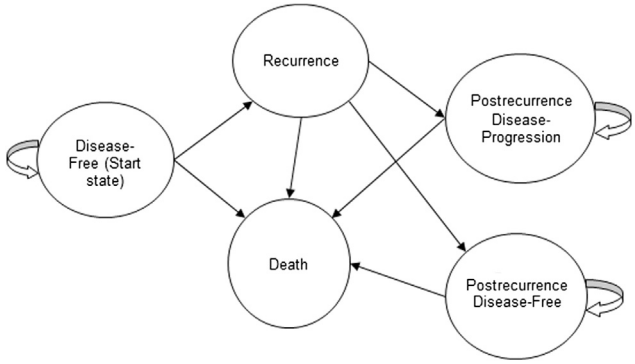

Fig. 1 – Markov model structure.

As mifamurtide is indicated for children, adolescents, and young adults, with the potential for a long life expectancy, a time horizon of 60 years was considered as the base case. Other time horizons were considered in the sensitivity analysis.

The number of patients exiting the disease-free state at the end of each 6-month cycle was governed by time-dependent transition probabilities of recurrence and death. Actual patient numbers, from patient-level data collected in the trial, were used to compute transition probabilities for each 6-month period, with patients lost to follow-up attributed to a health state based on the transition probabilities derived from those patients not lost to follow-up.

Patients who experienced a recurrence in the trial were not routinely followed up, and those who were lost to follow-up were reported as withdrawals. The clinical literature reported that the risk of survival postrecurrence was dependent on the site of recurrence, and that site was a determinant for achievement of disease- free status and survival postrecurrence. Of those patients in the trial whose disease did recur, approximately 85% of the patients in both treatment groups experienced disease recurrence at a pulmonary location or other (pleural, regional, radiation field, mediastinal, lymph node) sites. In the trial, approximately 50% of the patients had pulmonary metastases only.

Because the literature indicated that the risk of death postrecurrence was different for patients achieving disease-free or non–disease-free status postrecurrence, it was considered important to factor literature findings into the model and include an analysis of events postrecurrence.

Data from Ferrari et al. [17] were used to calculate remission rates from surgery or a combination of surgery and second-line chemotherapy. The Ferrari et al. study reported findings from 162 patients with recurrent osteosarcoma (75% of whom had lung metastases) who received first-line treatment, including

resection of the primary lesion and adjuvant chemotherapy with methotrexate, doxorubicin, cisplatin, and ifosfamide.

The estimates for survival postrecurrence also were taken from Ferrari et al. [17]. In that study, for those patients who failed to achieve complete surgical remission, postrecurrence survival did not differ according to the site of first recurrence but was influenced by the use of chemotherapy. The postrecurrence 1-year survival rate was 53% for patients who received chemotherapy versus 12% for patients who did not. Within 2 years, all patients were deceased. Postrecurrence survival rates at 1 year, 18 months, and 2 years were assumed to be 0.4, 0.18, and 0, respectively [17]. In patients who achieved complete surgical remission, postrecurrence survival was influenced by both relapse site and the length of the relapse-free interval ($\leq$24 or $>$24 months). The 5-year postrecurrence survival rates were reported as 20% (95% confidence interval [CI] 9%–30%) for recurrences occurring within 24 months or less and 60% (95% CI 46%–74%) for recurrences occurring after 24 months [17]. These rates were used in the model. Postrecurrence mortality rates were set to those of the age-matched general population if patients were disease free for 5 years.

Patients in each health state were attributed health-state utility values and costs within each cycle. A half-cycle correction was applied in the model.

Clinical Effectiveness

Clinical effectiveness data were taken from the randomized clinical trial reported by Meyers et al. [14], a primarily US-based, multicenter, phase III, open-label clinical trial. Given that this was the only significant trial of mifamurtide in the appropriate patient population, it was the only source for effectiveness evidence (e.g., extended evidence or mixed-treatment comparison would not be relevant). In brief, the trial recruited 678 patients with nonmetastatic osteosarcoma whose primary tumors were considered to be resectable, which included 16 patients who were deemed ineligible in the Meyer et al. study [14]. Although the true intention-to-treat population was 678 patients, compared with the trial reporting 662 patients in Meyer et al. [14], the study findings and conclusions were the same irrespective of inclusion or exclusion of ineligible patients. All patients were randomized at study entry to one of four groups (regimen A: methotrexate, doxorubicin, and cisplatin; regimen A+: regimen A plus mifamurtide; regimen B: methotrexate, doxorubicin, and ifosfamide; and regimen B+: regimen B plus cisplatin and mifamurtide). Mifamurtide administration was delayed until the maintenance (adjuvant) phase (week 12) following tumor resection. Detailed patient enrolment criteria and clinical results are described elsewhere [14]. In the base-case analyses presented here, data have been pooled across the two mifamurtide arms (regimens A+ and B+) and across the two nonmifamurtide arms (regimens A and B) of the trial.

The overall survival data for the intention-to-treat population in patients with nonmetastatic osteosarcoma in the trial showed that after a median follow-up of 7.7 years, adding mifamurtide to chemotherapy statistically significantly improved overall survival compared with chemotherapy alone ($P = 0.0313$). The hazard ratio for overall survival favored mifamurtide (hazard ratio = 0.72; 95% CI 0.53–0.98), with a 28% reduction in the risk of death.

Cost of Adjuvant Chemotherapy

In the trial, the total doses of methotrexate, cisplatin, and doxorubicin administered during induction and maintenance were identical in regimens A and B. The timings of cisplatin use between regimens A and B, however, were different [13,14]. Patients assigned to receive mifamurtide in the maintenance phase received twice-weekly intravenous infusions for 12 weeks, followed by once-weekly intravenous infusion for an additional 24 weeks, for a total of 48 infusions over 36 weeks. The number of doses received in the trial by each patient varied considerably—in fact, only 53% of the patients received the full 48-dose mifamurtide regimen. This is not unusual for pediatric experimental research, in which age is one of the most commonly cited predictors of early study dropout [18], and especially when considering the extension of the already significant standard treatment regimen with the introduction of mifamurtide. Because the efficacy data in the model are based on the number of actual mifamurtide doses administered and not the assumed 48 doses, the model default was set to the actual average of mifamurtide doses administered. A weighted average of 38 mifamurtide doses was calculated from trial data, and this number was used in the model's base case. Table 1 summarizes the unit costs for each of the agents in the adjuvant chemotherapy regimen, together with the unit cost of a mifamurtide dose.

Adjuvant chemotherapy in the United Kingdom is administered on an inpatient basis. According to the trial's dosing schema and expert opinion, a set number of inpatient days were attributed to each chemotherapy drug that also accounted for leucovorin rescue with methotrexate and mesna administration plus 24-hour rehydration postdose with ifosfamide. It was estimated that delivery of regimen A and regimen B (adjuvant chemotherapy) required 56 and 68 inpatient days, respectively. The trial's dosing schema also indicated that a proportion of mifamurtide doses required an outpatient visit, with no other adjuvant agent being scheduled for administration on these days. Because UK dosing schedules in clinical practice may vary from the dosing schedule in the trial, it was estimated that up to 30% of the doses may require an outpatient visit [19]. The average number of additional mifamurtide outpatient visits required was estimated to be 7, as calculated from the actual patient distribution of mifamurtide doses received. Uncertainty around this estimate was explored in a sensitivity analysis. Table 1 summarizes the unit costs associated with inpatient and outpatient visits for the delivery of adjuvant chemotherapy and mifamurtide.

Adverse Events

Only clinically relevant, treatment-differentiating adverse events were considered in the economic evaluation, that is, only those adverse events with a potentially higher incidence rate in the mifamurtide treatment arm than in the no-mifamurtide arm. Such events included infusion reactions, such as fevers and chills, and hearing loss. Clinical expert opinion considered the higher incidence of hearing loss in the mifamurtide group as a data anomaly, because hearing loss generally is associated with cisplatin use and the rates in the trial were consistent with those reported for cisplatin. In addition, differences in hearing loss were observed only in the A versus A+ arms (5% vs. 16%), not the B versus B+ arms (10% vs. 8%), adding further evidence that this was a data anomaly. Therefore, hearing loss was not included in the base-case analysis but was explored in a sensitivity analysis (mifamurtide: 15%; no mifamurtide: 8%). Cost estimates (Table 2) were derived from National Health Service reference costs. Expert opinion was used when estimating resource use for patients with hearing loss. Within 6 months of completion of the maintenance phase, patients experiencing hearing loss had a hearing aid fitted and a postfitting assessment. Thereafter, patients were assumed to have annual follow-up visits with an audiology department until the end of the 4-year postmaintenance phase, when a replacement hearing aid is fitted. Annual assessments continued after this replacement fitting.

Table 1 – Adjuvant chemotherapy and mifamurtide medication and resource costs.

Adjuvant chemotherapy and mifamurtide medication costs during the maintenance phase

Agent	Dose	Number of doses in regimen A	Number of doses in regimen B	Unit cost per dose (£)	Source
Doxorubicin	25 mg/m^2 per day	12	12	102.00	BNF 56 [20]
Cisplatin	120 mg/m^2	2*	4	100.44	BNF 56 [20]
Methotrexate	12 g/m^2	8	8	1369	BNF 56 [20]
Ifosfamide	1.8 g/m^2 per day	–	15	72.52	BNF 56 [20]
Mifamurtide	2 mg/m^2	38	38	2375	BNF 56 [20]

Adjuvant chemotherapy and mifamurtide administration costs

Description	Frequency	Unit cost (£)	Source
Inpatient visit to deliver adjuvant chemotherapy treatment in regimen A (first visit)	1	307	NHS reference cost 2007–08 (1SB14Z) [21]
Inpatient visit to deliver adjuvant chemotherapy treatment in regimen A	55	220	NHS reference cost 2007–08 (SB15Z) [21]
Inpatient visit to deliver adjuvant chemotherapy treatment in regimen B (first visit)	1	307	NHS reference cost 2007–08 (1SB14Z) [21]
Inpatient visit to deliver adjuvant chemotherapy treatment in regimen B	67	220	NHS reference cost 2007–08 (SB15Z) [21]
Outpatient visit for mifamurtide administration (30% of the mifamurtide doses are administered alone and require extra outpatient visit)	7	189	NHS reference cost 2007–08 (O/P specialty code 370) [21]
Pharmacy time to prepare a mifamurtide dose	1 h per dose	50	Clinical estimate

NHS, National Health Service.
* Two doses of cisplatin were administered during the induction phase for regimen A.

Resource Utilization

In the absence of resource-use data from the clinical trial, estimates of health care resource use were obtained from expert opinion and the European and American Osteosarcoma I study protocol [22].

In the model, resource use and monitoring costs were differentiated on the basis of health state, and the cost of routine monitoring was applied for each patient at the appropriate cycle, provided that the patient survived (Table 2). Routine monitoring costs ceased to be applied when patients moved from the disease-free state. As in clinical practice, routine monitoring of patients for weight assessment, clinical examination, thyroid function tests, and blood chemistry continued up to and beyond 12 years. Routine chest x-rays commenced after the first 4 months of the postmaintenance phase and were performed at every visit up to the end of year 5.

In the model, a transition to the recurrence state was conditional on a patient having no evidence of disease before recurrence. Therefore, transitions to this state were always from the disease-free state. Patients suspected of having a relapse from their routine chest x-ray performed during the disease-free state were considered asymptomatic. Patients stayed in the recurrence state for one cycle only before moving to one of the postrecurrence states. In this state, they incurred diagnostic costs (computed tomography scan, isotope bone scan, magnetic resonance imaging, blood tests, and central line insertion) as well as costs of additional surgery or chemotherapy (per clinical opinion). Second-line chemotherapy was assumed to be ifosfamide and etoposide administered on an inpatient basis for an average of five cycles (per clinical opinion).

Table 2 outlines the costs associated with recurrence diagnosis and surgery. Two outpatient visits for diagnostic evaluation and a further 3-day elective inpatient stay for surgery were assumed. These costs were applied for each patient at the point of recurrence in the model.

Patients were assumed to have palliative care when in the postrecurrence disease-progression state. No evidence could be found to quantify the resource utilization for palliative care in patients with osteosarcoma in the United Kingdom. For the economic evaluation, the cost of palliative care (£3481) for patients in disease progression was assumed to be the average of the mean National Health Service cost across all cancers [25]. Palliative care costs were incurred at the point of death in the model.

Health-Related Quality of Life

Although cost-utility analysis is the framework of economic evaluation preferred by UK health technology assessment bodies, no cost-utility analyses have been conducted in osteosarcoma. There have been no suitable utility values published for adolescents with the disease. In the absence of trial-based or published estimates, the utilities used in the model were obtained from a review of NICE appraisals of cancer technologies, including treatments of colon, colorectal, renal cell, and prostate cancer, myeloid leukemia, and glioma, with 0.85 being representative of the health-related quality of life of patients who are deemed as disease free following cancer treatment. The specific base-case utilities and rationale for the choice of utility for each health state are provided in Table 3, with alternative scenarios that were investigated in sensitivity analysis for impact on cost-effectiveness.

The disutility for hearing loss was not captured by the health-state utilities outlined in Table 3 and hence has been included as an additional disutility factor across the health states for patients

Table 2 – Monitoring, resource, and adverse event costs.

Frequency of routine monitoring in the disease-free state

Timing of visit following the maintenance phase	Frequency
Up to 4 mo	Monthly
5 mo to 1 y	Every 2 mo
Year 2	Every 3 mo
Years 3 and 4	Every 4 mo
Year 5	Every 6 mo
Year 6 onwards	Once a year (the EURAMOS 1 study [22] required twice yearly monitoring but a UK expert opinion noted that this is not typical UK practice)

Recurrence diagnostic and surgery resources and unit costs

Resource	Frequency	Unit cost (£)	Source
Diagnosis			
CT scan	1	116	NHS reference cost 2007–08 [21] (RA11Z)
MRI	1	214	NHS reference cost 2007–08 [21] (RA02Z)
Isotope bone scan	1	164	NHS reference cost 2007–08 [21] (RA36Z)
Outpatient visits	2	189	NHS reference cost 2007–08 [21] (O/P specialty code 370)
Inpatient visit for central line insertion	1	4288	NHS reference cost 2007–08 [21] (EA36B, catheter 18 y and under)
Surgery			
Salvage surgery (pulmonary) (3-d inpatient stay)	1	1797	NHS reference cost 2007–08 [21] Equal to average of three elective inpatient HRGs (DZ09A, DZ09B, and DZ09C)
Salvage surgery (nonpulmonary) (3-d inpatient stay)	1	2194	NHS reference cost 2007–08 [21] Equal to average of three elective inpatient HRGs (HD36A, HD36B, and HD36C)
Annual cost of endoprosthesis	NA	1091	Cost derived from Grimer [23], cost uplifted to 2006 via the consumer price index [24]

Costs of treatment-differentiating adverse events during maintenance

Adverse event	Mifamurtide incidence (%)	No mifamurtide (%)	Treatment during the maintenance phase	Unit cost (£)	Source
Infusion-related influenzalike symptoms (chills and fever)	98	0	Paracetamol 0.5–1 g every 4–6 h to a maximum of 4 g daily	1.91	BNF 56 [21]: paracetamol 500 mg. Net price: 16 tablets = £0.17; 32 tablets = £0.46; 100 tablets = £1.91 (100 tablets per patient)
Hearing loss (objective or subjective)	15	8	One audiometry assessment	50.00	NHS reference cost 2006–07 [21] (AS1A: fitting of hearing aids and counseling assessment)

CT, computed tomography; HRGs, Healthcare Resource Groups; MRI, magnetic resonance imaging; NA, not applicable; NHS, National Health Service.

Table 3 – Utilities for modeling.

Disease state	Base-case utility	Source/rationale
Disease progression	0.39	NICE HTA review. The HTA review provided an estimate of 0.44 for the disease progression to death category, which was adjusted by the –12% correction factor, as given below
Disease free	0.85	NICE HTA review
Recurrence	0.61	NICE HTA review. The HTA review provided an estimate of 0.69 for the disease-progression/recurrence category. A correction factor of –12% was applied, on the basis of the ratio for the average utility for the disease-free state in the EQ-5D questionnaire survey and Alessi et al. [27] (0.75) and the disease-free category in the NICE HTA review (0.85)
Disease-free postrecurrence	0.85	Assumed to be the same as the disease-free value
Disease progression postrecurrence	0.39	Assumed to be the same as the disease-progression value.
Death	0	

EQ-5D, EuroQol five-dimensional; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence.

experiencing this event. A single study was identified that contained a disutility factor of –18% for hearing loss in patients with cancer [26], although no such study exists specifically for patients with osteosarcoma. This factor represents a significant decrement in utility and is associated with the need for a hearing aid. The factor, however, may be an overestimate for hearing loss due to osteosarcoma-related chemotherapy; clinical opinion did not suggest that any hearing impairment in patients with osteosarcoma always resulted in a hearing aid and a resulting disutility of 0.18 [15]. Given the absence of data for osteosarcoma, this value was considered to be a conservative estimate and was assessed in a sensitivity analysis.

Sensitivity Analysis

To test the uncertainty of some of the model assumptions, a series of univariate analyses were performed on several parameters. Costs could vary by 40%, excluding drug costs, which were fixed. Mortality rates postrecurrence, as well as surgery and second-line chemotherapy at recurrence, were assumed to vary within their 95% CIs. Recurrence rates and quality-of-life utility values varied between their 95% CIs, derived from assuming that each utility value followed a beta statistical distribution. The total number of individuals used to derive the utility values was based on the number of individuals in the Alessi et al. [27] study. Discounting was varied between 0% and 6%.

In the probabilistic analysis, key model parameters were sampled from parametric distributions to generate 10,000 estimates of the costs and effects in each arm, from which the probabilistic mean incremental cost-effectiveness ratio (ICER) and 95% CIs were estimated. The transition probabilities of recurrence and death from the disease-free state, which were derived from the trial data, were sampled from a Dirichlet distribution, using a series of conditional beta distributions, a method that corresponds to the decomposition of a multibranch node into a series of conditional dichotomous nodes [28]. Transition probabilities to and from the postrecurrence disease states and utility weights were sampled from beta distributions derived from patient numbers [17]. Costs were sampled from a gamma distribution defined by the mean and assuming a standard error of one fifth of the mean [29].

Outputs from the probabilistic sensitivity analysis were used to generate cost-effectiveness acceptability curves, to assess the probability of cost-effectiveness at different thresholds representing UK society's willingness to pay.

Results

Base-Case Results

The base-case results presented in Table 4 compare maintenance chemotherapy plus adjuvant mifamurtide treatment (both regimens A and B) to maintenance chemotherapy alone. The base-case results were based on a time horizon of 60 years. Over this time frame, patients receiving mifamurtide benefited from an average additional 3.95 years of life and 1.34 quality-adjusted life-years (QALYs) than did patients receiving maintenance chemotherapy alone. The drug cost attributable to mifamurtide was £91,189; there also was an increased overall use cost of £1,181 for patients receiving mifamurtide, mainly due to the increased number of outpatient visits required for the administration of mifamurtide.

Table 4 – Base case discounted per patient mean costs and effects.

Results	Mifamurtide (£)	No mifamurtide (£)	Mifamurtide vs. no mifamurtide (£)
Mifamurtide drug cost	91,189	0	91,189
Adjuvant chemotherapy cost	26,205	26,205	0
Resource-use cost	6,458	5,277	1,181
Total costs	123,852	31,481	92,371
Life-years	19.70	18.13	1.57
Cost per life-years gained			58,737
QALYs	16.72	15.38	1.34
Cost per QALY			68,734

QALY, quality-adjusted life-year.

Table 5 – New base case based on a discount rate of 1.5% for health effects and 3.5% for costs.

Results	Mifamurtide (£)	No mifamurtide (£)	Mifamurtide vs. no mifamurtide (£)
Mifamurtide drug cost	91,189	0	91,189
Adjuvant chemotherapy cost	26,205	26,205	0
Resource-use cost	6,458	5,277	1,181
Total costs	123,852	31,481	92,371
Life-years	29.53	26.95	2.58
Cost per life-year gained			35,765
QALYs	25.07	22.87	2.20
Cost per QALY			41,933

QALY, quality-adjusted life-year.

The cost-effectiveness of maintenance chemotherapy plus mifamurtide over maintenance chemotherapy alone was estimated to be £68,734 per QALY and £58,737 per life-year gained.

Sensitivity Analysis: The Discount Rate

Cost-effectiveness estimates were most sensitive to the discount rate for outcomes because for a young population, the long-term benefits of mifamurtide treatment were heavily discounted. That is, the majority of the treatment costs were incurred in the first year of the model, but the clinical outcomes were realized over the entire time horizon.

NICE [16] currently recommends an annual discount rate of 3.5% for both costs and outcomes for the reference case. After a reappraisal of mifamurtide, however, NICE issued further guidance on discounting of health benefits in special circumstances. The new guidance by the NICE Appraisal Committee now states that "where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs." This category applies to mifamurtide; hence, a new base case was developed by using these new discount rates. The results are presented in Table 5.

Using the new discount rates as recommended by NICE, a sensitivity analysis showed that patients receiving mifamurtide benefited from an average additional 2.20 QALYs than did patients receiving maintenance chemotherapy alone. This resulted in an ICER of £41,933 per QALY and £35,765 per life-year gained.

Sensitivity Analysis: Other Parameters

In the univariate analysis, the results were sensitive to the health-state utility for the disease-free state and the number of doses of mifamurtide given to the patient. When the utility was decreased from its default value of 0.85 to 0.75, the resulting ICER was £47,582 per QALY. Changing the time frame of the analysis to 40 years also had a noteworthy effect on the ICER, increasing it to £55,586 per QALY.

The sensitivity analysis also explored the costs applied to the management of hearing loss, as well as its impact on health-related quality of life. Incorporating the adverse event of hearing loss assumed that 15% of the patients receiving maintenance chemotherapy plus mifamurtide and 8% of the patients receiving chemotherapy alone had hearing impairment. This assumption affected both the costs and QALYs because a utility decrement of 18% was applied to these patients, along with extra resource costs. The resulting discounted ICER increased to £51,545 per QALY. The univariate sensitivity results are presented in Table 6.

Sensitivity analysis indicated that the ICER was relatively insensitive to other inputs explored.

The uncertainty about the effect of interaction between ifosfamide and mifamurtide on the trial results was explored in a subgroup analysis. The sensitivity analysis results for the treatment groups with and without ifosfamide underscored the importance of this question in regard to the cost-effectiveness of mifamurtide. For regimens A+ versus A, results for the base-case scenario were £103,343; for regimens B+ versus B, results for the base-case scenario were £26,872. The Study INT-0133, however, was not powered to compare regimens A+ versus A and B+ versus B separately and overall survival differences were not statistically significant for the

Table 6 – Univariate sensitivity analysis.

Variable	Value		Results	
	Low	High	Low	High
Discount—outcomes	0%	6%	£26,995	£112,536
Discount—cost	0%	6%	£42,009	£41,925
Utility—disease-free	0.75	0.94	£47,582	£39,584
Utility—disease-progression	0.25	0.54	£41,937	£41,929
Utility—disease recurrence	0.46	0.75	£41,877	£42,024
Adjustment for multiple vials*	NA	1.05	NA	£44,003
Cost of an outpatient visit for mifamurtide dosing	£113	£265	£41,680	£42,187
Hearing loss	None	18%	NA	£51,545
Time frame	40 y	NA	£55,586	NA

NA, not applicable.
* Increase in the number of mifamurtide doses.

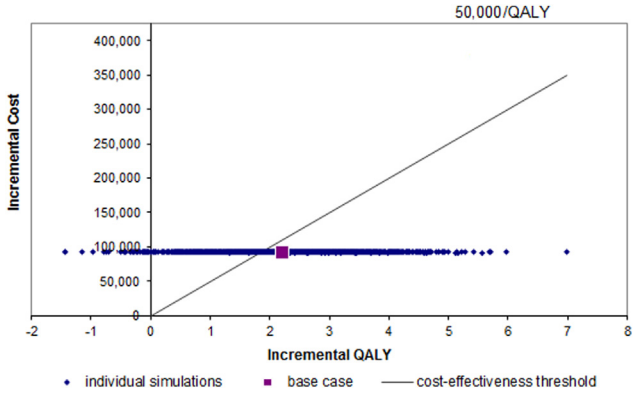

Fig. 2 – Simulations of mean incremental total costs versus benefits for mifamurtide versus no mifamurtide (outcome discount rate = 1.5%). QALY, quality-adjusted life-year.

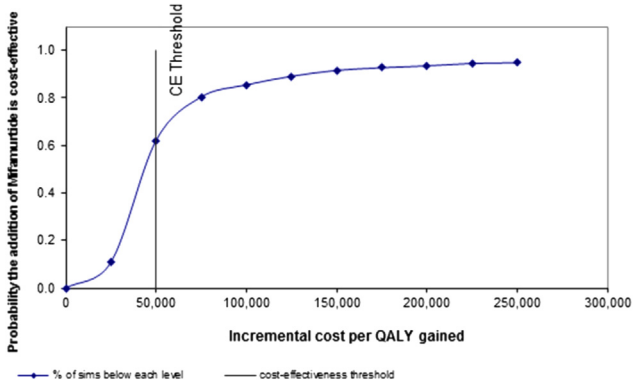

Fig. 3 – Cost-effectiveness acceptability curve for mifamurtide versus no mifamurtide. CE, cost-effectiveness; QALY, quality-adjusted life-year; sims, simulations;

two subgroups. Thus, as NICE concluded, the more appropriate comparison was the combined analysis of all the Study INT-0133 data [15].

The probabilistic analysis of the base case suggested that there was a 23.5% probability that the ICER would fall below a threshold value of £30,000 per QALY and a 62.5% probability that it would fall below a threshold value of £50,000 (see Figs. 2 and 3).

Discussion

We have used data from a trial conducted in the 1990s to evaluate the cost-effectiveness of mifamurtide as an add-on to multiagent chemotherapy versus multiagent chemotherapy alone for patients with high-grade, resectable, nonmetastatic osteosarcoma after macroscopically complete surgical resection. We also have attempted to identify all published data that could inform the model, particularly in relation to postrecurrent health states. The model presented here is the first economic evaluation published for osteosarcoma, an ultra-orphan disease.

The results were highly sensitive to the discount rate for outcomes, given that the majority of the treatment costs are incurred within the first year of the model but that the clinical outcomes are realized over the entire model time horizon. Using the standard NICE discount rate of 3.5% for outcomes, the incremental benefit of 3.95 life-years and 1.34 QALYs due to the addition of mifamurtide, coupled with the incremental costs of £92,371, resulted in an ICER of £68,734 over the 60-year time frame. Following new guidance from NICE, however, in the special case of mifamurtide, a discount rate of 1.5% is recommended for outcomes, which resulted in an ICER of £41,933. The ICER is favorable and represents a cost-effective option when compared with other orphan and ultra-orphan drugs, for which prices and the corresponding cost-effectiveness estimates are high (see Table 7) [30].

There has always been some debate over the rates of discounting that should be used in a cost-effectiveness analysis, whether the discounting should be uniform or differential, and whether discount rates should vary over time [31]. Opponents of using a uniform discounting approach have argued that using uniform discounting assumes that the relationship between costs and life-years (and hence QALYs) remains independent of time, which may not necessarily be the case. Another argument for differential discounting, supporting a view that health benefits should not be discounted at all, was the possibility of inadvertent double discounting of benefits [32,33]. These authors argued that health-related outcomes such as quality of life may already have been incorporated into an individual's time preference, especially when utility is measured by using the time trade-off or standard gamble method. Thus, they conclude, if health outcomes also are discounted in the future, the value of future benefits of an intervention will be underestimated.

The most commonly used method of discounting adopted by the reimbursement authorities, such as NICE, is uniform discounting, using a constant nonzero discount rate (commonly 3% or 5%). Severens and Milne [31] argued that this method leads to prioritization of immediate treatment at the expense of

Table 7 – Some ultra-orphan drugs in current use [30].

Product	Condition	Prevalence	Preliminary estimated ICER (£ per QALY)
Agalsidase beta (Fabrazyme)	Fabry's	200	203,009
Imiglucerase (Ceredase)	Gaucher's (types I and III)	270	391,244
Laronidase (Aldurazyme)	Mucopolysaccharidosis (type 1)	130	334,880
Miglustat (Zavesca)	Gaucher's (type I)	270	116,800
Nonacog alfa (BeneFIX)	Hemophilia B	350	172,500
Iloprost (Ventavis)	Primary pulmonary hypertension	100	23,324
Mifamurtide	High-grade, resectable, nonmetastatic osteosarcoma after macroscopically complete surgical resection	58	68,734 (original base case) 41,933 (using 1.5% outcomes discount rate)

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

prevention and thus works against long-term public health measures, including some evidence-based screening and pediatric vaccination programs. Because osteosarcoma primarily affects the young, this argument is valid in the case of mifamurtide. Severens and Milne [31], however, also stated that variable discounting rates of both costs and benefits can be adopted as a methodology without violating the theoretical principles of uniform discounting. A variable discounting approach for health outcomes, when compared with a uniform discount rate over time, would clearly support health care programs that incur costs now but have future health benefits. Such an example would be vaccines, where there is typically a long time lag between vaccination and its benefit (avoidance of later illness), a scenario similar to mifamurtide treatment. The discount rate used in an economic evaluation of a vaccine is particularly important, and such analyses often incorporate 1.5% and 0% discount rates [34].

The rarity of a disease means that development costs must be recouped from drug sales to a limited number of patients worldwide, with consequently high per-patient acquisition costs [35]. This means, however, that it is virtually impossible for these treatments to meet conventional criteria for cost-effectiveness. Many researchers have argued for a special status for ultra-orphan and orphan drugs, in terms of applying a different value to health gain obtained by patients with those conditions [35–37]. Furthermore, doubts have been expressed about whether standard methods of health technology assessment are entirely suitable for the evaluation of drugs for rare diseases [38]. A number of options to address resource allocation issues for ultra-orphan drugs have been suggested, including more focus on the societal value of these drugs, different mechanisms of funding, and QALY weighting according to disease prevalence. The literature also suggested that a majority of the general population had a preference for putting a greater weight on health gains accrued by children, by severely ill patients, and by the socioeconomically disadvantaged [39].

A number of researchers, however, have argued that awarding a special status to ultra-orphan drugs may impose substantial and increasing costs on the health care system, with these costs invariably being borne by patients with more common diseases [40]. Other potentially relevant issues that remain outside the cost-effectiveness framework include the poor prognosis for patients with osteosarcoma and the absence of other effective treatment options.

Obtaining accurate cost-effectiveness estimates is often more difficult for ultra-orphan drugs than for others drugs, and this can produce considerable uncertainty regarding cost-effectiveness. The evidence base for orphan drugs is considered to be too sparse to allow estimates of cost-effectiveness. The clinical evidence informing our analysis was derived from one large, prospective, randomized, phase III trial. Although the trial generally was well conducted, there were several methodological issues raised by NICE, but none was considered substantial enough to decline approval of the product [15]. These included delayed administration or nonadministration of mifamurtide and an imbalance in histological response to neoadjuvant therapy between treatment groups, the disparity being particularly pronounced for patients assigned to regimen A+, who had a greater proportion of tumors showing a poor histological response, which, as NICE commented, may have disadvantaged mifamurtide. The effect of these methological issues raised by NICE has led to further uncertainty, and the single source of data for efficacy parameters means that any biases within the trial will be reflected in the cost-effectiveness analysis presented here.

Although recurrence was an end point in clinical trial, information pertaining to a patient's disease-free or disease-progression status after recurrence (with the exception of death) was not collected consistently in the study. Assumptions regarding resource and outcomes postrecurrence were derived from a single source [17] in the absence of other available data. Again, any biases within this study will be reflected in the cost-effectiveness analysis presented here.

There is an absence of published data on the utilities associated with the treatment of osteosarcoma. In our analysis, we have used data from our review of the utilities used in independent economic models developed by the NICE Assessment Group for published or ongoing cancer technology appraisals. We believe that this is a comprehensive approach to ascertaining utilities in this ultra-orphan disease, where there is minimal information. Other health-related quality-of-life benefits, however, may not have been adequately captured in the estimated gains used in the QALY calculation—such as the utility of carers, particularly for patients for whom treatment is not successful.

Conclusions

This is the first economic cost-effectiveness analysis of mifamurtide for the treatment of high-grade, resectable, nonmetastatic osteosarcoma. By using data from Study INT-0133, the model demonstrated that patients with newly diagnosed, high-grade, resectable, nonmetastatic osteosarcoma experienced improved survival outcomes when mifamurtide was added to a three- or four-agent chemotherapy. Such a benefit is particularly important, given the huge unmet medical need and the lack of progress in improving outcomes for patients with osteosarcoma over the last 20 years. While results were highly sensitive to the discount rate for outcomes, given the long time horizon of benefit accrual, mifamurtide's ICER is favorable and represents a cost-effective option compared with other orphan and ultra-orphan drugs, for which prices and the corresponding cost-effectiveness estimates are high. Obtaining accurate cost-effectiveness estimates, however, is often more difficult for ultra-orphan drugs than for other drugs, which can produce considerable uncertainty regarding the cost-effectiveness.

Further research is required to address the parameter uncertainty of the analysis presented here, as well as to understand and address the shortcomings of economic evaluations of ultra-orphan drugs, particularly those used to treat childhood diseases.

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